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# Expectations and advice from regulators to industry how to use the new framework of estimands in clinical trials



CDDF MULTI-STAKEHOLDER WORKSHOP  
INNOVATION IN ONCOLOGY CLINICAL TRIAL DESIGN

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## Views expressed

- my own, based on my experience at MEB as statistical assessor
- not necessarily those of MEB

## Examples

- based on true examples
- but are no true cases

## Aim

- what will streamline, in my view,
  - SA (scientific advice) discussions,
  - MAA (marketing authorization applicant) procedures assessment
  - in oncology trials
  - expectations regarding estimands discussion
- However, not hewed in stone,  
time will learn ...interplay in process between
  - industry, doctors, regulators, patients, health care insurers, insights from medical research, organisation of care, ...

## Intercurrent events

causing missing information as to the situation when patients would have adhered to randomised treatment and to assessment as per protocol until end of trial

## Intercurrent events for time-to-event endpoints

- No different from continuous, binary, rate outcomes:
  - Change in protocol treatment
    - discontinuation of treatment especially: treatment switching
      - lack of efficacy: e.g. progression
      - AE
      - (substantial) resolution of disease
      - other
    - Change in concomittant therapy (additional medication)
  - Leave the trial (permanently):
    - withdrawal by patient or by physician (for reasons as above)
    - Lost-to-followup
    - Terminal event like death usually incorporated in endpoint (PFS, OS)
  - No protocol assessment
    - missed visits
    - undocumented (spontaneous) assessments
      - undocumented progression altering course/treatment disease

Intercurrent events:

- continu./bin./rate outcomes: currently often 'hidden' in missing data,
- time-to-event outcomes: currently often 'hidden' in censored data
  - censoring for start new anti-cancer therapy
  - Censoring for > 1 missed visits
  - Censored for undocumented progression

Informative censoring?

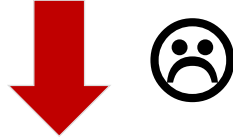
- (Note: censoring at end-of-trial are not intercurrent)

- Set rules regarding
  - data collection wrt intercurrent events (in design)
  - handling of intercurrent design (in analysis)
- Example:
  - Censor control patients who switch to experimental treatment
  - No data collection after switch

- However: handling of intercurrent events in design and analysis
  - dictates which effect is estimated (which question is answered)
  - under which assumptions
- Example (censor at switch):
  - Effect “when no control patient would have switched to experimental treatment” (*Hypothetical estimand*)
  - Unbiased for this effect under the assumption:
    - “patients in control group that do not switch are representative for those that do switch” (censoring due to switching is non-informative)

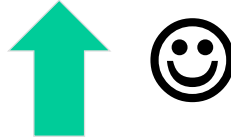


- Handling of intercurrent events in design/analysis



Effect estimated / Question answered (*estimand*)

- Handling of intercurrent events in design/analysis



Effect to be estimated / Question to be answered (*estimand*)

- Discussion with stakeholders (regulators, industry, ..) about
  - which** estimand is primary and **why**
  - how** design and analysis will estimate it (*estimator*)
    - under which assumptions
  - Sensitivity analyses **per estimand**
    - i.e. different assumptions (different estimators) for the same question
  - Possibly: which secondary/other estimands
    - For other stake holders / broader view
- scientific advice
  - especially if no consensus (from e.g. guidelines)

- PFS primary endpoint
  - Censoring rules / data collection after censoring:
    - what is the implied estimand?
    - Which analyses address the same question (estimand) and which different estimands?
  
- OS primary endpoint
  - cross-over of control patients to experimental treatment
  - Switch to treatment that changes course of disease substantially e.g.
    - (completely) different mechanism of action
    - (completely) different efficacy (safety)
  
    - For example: stem cell transplantation
    - (underlying consideration: some stakeholders consider it 'unfair' to use an treatment policy estimand then)

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PFS

- EMA:
  - Appendix 1 to GL on evaluation of anticancer medicinal products in man (CHMP/EWP/205/95 rev.3)
- progression date= first evidence of objective progression
- Regardless of violations, discontinuation, change of therapy.
- But:
  - If, for a particular study, a different approach is considered to be more appropriate, a justification is expected and CHMP Scientific Advice agreement is recommended at the planning stage.
- => no censoring for violations, discontinuation, change therapy
- => treatment policy estimand (preferred)

- FDA:
  - GfI: Clin. trial endpoints for the approval of cancer drugs and biologics
- progression date = earliest time of observing any progression
  - without prior missing assessments and censoring at the date when the last radiological assessment determined a lack of progression.
- “For instance, for the primary analysis, patients going off-study for undocumented clinical progression, change of cancer treatment, or decreasing performance status can be censored at the last adequate tumor assessment. The secondary sensitivity analysis would include these dropouts as progression events.”

- => censoring when going off study for
  - undocumented clinical progression,
  - change of cancer treatment, or
  - decreasing performance status
- => going of study: no PFS data collection implied after censoring
- => *hypothetical estimand*  
 “effect if no patient would switch to another treatment and stay in the study until documented clinical progression”
- (Kaplan-Meier/Cox regression)  
 unbiased for this effect under the assumption:  
 “patients that do *\*not\** switch/undocu.PD/PS ↓  
 are representative for those that do switch/undocu.PD/PS ↓

- Often many sensitivity analyses presented

Scenario 1: If disease progression was documented between scheduled visits, the date of the next scheduled visit was used as the date of progression.

Scenario 3: If the patient started new antineoplastic therapy with or without subsequent progression/death event, the patient was censored at the date of the last disease assessment before the start of antineoplastic therapy.

Scenario 4: If the patient started new antineoplastic therapy (with or without subsequent progression/death event), the patient was treated as progressed at the date of last disease assessment before the start of antineoplastic therapy.

Scenario 5: If death or progressive disease occurred after more than 1 missed visit, the patient was censored at the last disease assessment before the missed visits.

Scenario 6: If death or progressive disease occurred after more than 1 missed visit, the patient was censored at the last disease assessment before the missed visits. If the patient started new antineoplastic therapy with or without subsequent progression/death event, then the patient was censored at the date of the last disease assessment before the start of antineoplastic therapy.

- May give a false sense of consistency as to the primary estimand (question at hand) if these sensitivity *align* but actually *address different* estimands (questions)
- May give a false sense of inconsistency if these do *not align* because they are *addressing different* estimands/questions



## Advice / expectations:

- Clarify which estimand / question is addressed
- Especially for sensitivity analyses
- Present per estimand (question)
  - the primary analysis (estimator)
  - The sensitivity analyses (estimators) explaining
    - that the same estimand (question) is addressed
    - which assumptions are varied

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OS

- Many intercurrent events:
  - always subsequent therapy:
    - may argue whether this is intercurrent or not
    - i.e. an active stopping of randomised treatment to start a new therapy
- Often a treatment policy estimand (implicit) chosen
  - so intercurrent events and subsequent therapy no issue
- Although assessment of (difference in) subsequent therapies
  - Some acknowledgement of part of difference in survival due to difference in subsequent therapies
  - *hypothetical estimands* (e.g. “what would be the effect if similar or no subsequent therapy”) in principle may be desirable for some stakeholder, but difficult to estimate
- Exceptions where not only treatment policy questions are used:
  - switch to experimental treatment (“cross-over”)
  - switch to therapies that substantially change course of disease

- Two estimands (implicitly) used
  - Treatment policy effect
  - Effect if no cross-over would have been available (hypothetical estimand)
    - Latter often proposed by Sponsor for ‘pure efficacy of randomised trt’
  
- Issues
  - hypothetical estimand *post-hoc proposed* when treatment policy OS fails
  - Estimators for this hypothetical estimand typically require strong assumptions
    - IPCW: no unmeasured confounders
    - RPSFT: Main assumption: (relative) treatment effect when switching is the same as time of randomisation
    - Two-stage: switch at designated ‘secondary baseline’ (e.g. progression) and no unmeasured confounders at this secondary baseline

## Advice/expectations:

- Preplan (and discuss) which estimand is primary and why
- Preplan to collect extra data to motivate that assumptions of estimators are plausible
- Avoid switch to experimental therapy (!?)
- If Kaplan-Meier curves converge, conclusion can still be that data justify that postponing drug until progression is viable.
  - so provide other arguments data that shows that early start is favorable and collect data for that

## Example

- Disease: leukaemia
- EU trial, but different standard of care in regions
  - west-EU: stem cell transplantation part of standard of care
  - east-EU: stem cell transplantation much much less available
- Treatment policy estimand was (implicitly) preplanned:
  - OS including transplant
  - No censoring for transplant
- Treatment policy OS:
  - not clinically relevant difference,
  - not statistically significant

- Post hoc proposed: hypothetical estimand:
  - “OS when no transplant would have been available”
  - Censoring for transplant
    - with inverse probability weighting on certain characteristics to ‘replace’ a patient having transplant by a patient not having transplant with those characteristics similar (IPCW).
  - No unmeasured confounders assumption:
    - prognosis, switch, and time of switch are captured by characteristics used in IPCW
- data-collection (timing and type of variables) not preplanned and not (fully) convincing that ‘no unmeasured confounders’ assumption is plausible
- Clinically relevant, statistically significant difference found .....may be relevant for east-EU, but not for west-EU ?!

## Advice/expectation

- A priori discussion which estimand primary,
  - for which stakeholder
- Preplan data-collection/design accordingly
  - Here:  
A priori data collection to make 'no unmeasured confounders' assumption needed by IPCW stronger



## Estimands:

- different way to look at questions that were relevant before
  - what question are we trying to answer,
  - under which assumptions and
  - how to translate this is good design and analysis
- Reframing good practice we (at least partially) did before
- Enforcing clarity
- empowering stake holders

Thank you for your attention

